REMARKS

Claims 1, 5-13, 19-27, and 42-45 are pending in the subject application. No claim has been added, canceled or amended herein.

In view of the remarks and arguments set forth below, applicants submit that the grounds of the Examiner's rejections made in the June 4, 2004 Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these rejections.

The Claimed Invention

This invention is directed to a composition which comprises an admixture of two compounds. One compound retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell. The other compound retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate. The relative mass ratio of the compounds in the admixture ranges from about 100:1 to about 1:100, and the composition is effective to inhibit HIV-1 infection of the CD4+ cell. The invention also provides a method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an amount of this composition effective to inhibit HIV-1 infection of the CD4+ cell.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1, 5-13, 19, 21-26 and 42-45

The Examiner rejected claims 1, 5-13, 19, 21-26 and 42-45 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a composition and method using the composition comprising an admixture of two peptidyl compounds, allegedly does not reasonably provide enablement for an admixture of two non-peptidyl compounds. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Examiner stated that the breadth of the claims as written encompasses any compound that binds gp120 or gp41 that is not a peptide. The Examiner also stated that the nature of the invention is the inhibition of HIV-1 entry into CD4+ cells. According to the Examiner, the state of the prior art has examples of non-peptidyl agents that inhibit HIV-1 infectivity although not necessarily by binding gp120 or gp41. The Examiner further stated that, for example, Vitetta (WO 92/01451) teaches a method for killing HIV-infected cells by administering chloroquine in combination with other agents such as anti-HIV immunotoxins (CD4-based immunotoxins or anti-gp41 or anti-gp120 based immunotoxins). The Examiner also stated that Vitetta teaches that the two compounds work synergistically to effect selective killing of HIV-infected cells (citing the abstract). The Examiner further stated that Vitetta does not disclose the mechanism of chloroquine, merely that it kills HIV-infected cells. The Examiner additionally stated that, furthermore, Oroszlan *et al.* (U.S. Patent No. 5,668,149) teaches that the exact mechanisms by which chloroquine inhibits HIV infectivity has yet to be determined by direct analysis of HIV gp120/160 from chloroquine-treated cells (citing column 8, lines 1-4).

According to the Examiner, applicants are claiming that non-peptidyl agents inhibit HIV entry by binding to gp120 or gp41, but that, however, the state of the art does not support that such an agent or mechanism is known. The Examiner asserted that the level of one of ordinary skill is high but that the predictability of the art of inhibiting HIV-1 entry is poor, given the lack of successful *in vitro* to *in vivo* attempts. The Examiner quoted Gait *et al.* (1995) Progress in anti-HIV structure based drug design, *Trends in Biotechnology* 13(10): 430-437, that "effective regimens for the prevention of the progression to clinical symptoms of acquired immune deficiency syndrome (AIDS) and the treatment of AIDS patients have not yet been developed." The Examiner stated that the guidance in the specification does not mention any potential non-peptidyl compounds. The Examiner also stated that there are no working examples from which to ascertain candidate compounds for use in the invention. The Examiner concluded that the quantity of experimentation needed to make or use the invention would be undue due to the lack of information provided regarding the compounds.

In response, applicants respectfully traverse this rejection. Applicants acknowledge the Examiner's statement on page 2 of the Office Action that the specification is enabling for a composition comprising an admixture of two peptidyl compounds, and a method of using such a composition. Applicants respectfully urge that the specification is also enabling for a composition comprising an admixture of two non-peptidyl compounds, and a method of using same, for the reasons presented below.

Applicants note that the legal standard for enablement is set forth in 35 U.S.C. §112, first paragraph. This section requires that:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

> pertains, or with which it is most nearly connected, to make and use the same, ...".

The requirements for enablement are further explicated in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988):

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. ... Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the Board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (emphasis added, footnotes omitted)

Applicants note that not all the *Wand* factors must necessarily be considered: "it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts ..." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016 (Fed. Cir. 1991).

Applicants emphasize that the specification provides a rational screening strategy based on the resonance energy transfer (RET) assay for identifying compounds that inhibit fusion of HIV-1 (or a cell expressing HIV-1 env glycoproteins to CD4+ cells. See, *inter alia*, page 23, line 17-28; page 25, line 21 to page 26, line 1. Moreover, applicants note that the RET assay was well known to those skilled in the art at the time the instant invention was made, details of the assay having been disclosed in PCT International Publication No. WO 95/16789, published June 22, 1995, and Litwin et al. (1996) J. Virol. 70: 6437-6441.

Applicants contend that the RET assay provides a powerful and flexible method for identifying, without significant or undue experimentation, inhibitors of HIV-1 infection of CD4+ cells, even without any prior knowledge of the chemical structures of these compounds. An example of the utility of the RET assay in identifying compounds which inhibit HIV-1 infection, in the absence of any prior knowledge of the structure of these compounds, is provided by PCT International Publication No. WO 02/079186 A2, published October 10, 2002. Applicants attach hereto as **Exhibit A** a copy of the cover page and pages 1-3 and 59-61 of WO 02/079186 A2. There, the objective was to identify compounds that inhibit entry of HIV-1 into target cells by binding to the CCR5 receptor, optionally without blocking chemokine binding, and thereby preventing the interaction of HIV gp120 and CD4 with this receptor (see page 2, lines 11-15 of the published PCT application). Using the RET assay as described by Litwin et al. (1996), numerous non-peptidyl compounds that inhibit HIV-1 infection were successfully identified (see, *inter alia*, page 1, lines 2-10; page 2, line 11 to page 3, line 19; page 59, lines 18-33; page 61, lines 3-13).

Although WO 02/079186 A2 was published after the filing date of the subject application, applicants maintain that it constitutes evidence demonstrating that the RET assay, as known to a skilled artisan at the filing date of the subject application, enabled persons skilled in the art to identify non-peptidyl inhibitors of HIV-I infection of suitable target cells. Thus, applicants maintain that one skilled in the art could readily practice the invention claimed herein without undue experimentation by using the RET assay in a routine screen to identify non-peptidyl compounds that inhibit fusion of HIV-1 or cells expressing HIV-1 env glycoproteins to CD4+ cells.

Applicants further maintain that once these non-peptidyl inhibitors are identified by routine screening, equally routine biochemical assays can be used to delineate the mechanism of action of these inhibitors. Accordingly, such routine assays will identify non-peptidyl compounds that, *inter alia*, (1) retard binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of a CD4+ cell and thereby inhibit attachment of HIV-1 to the CD4+ cell, and (2) bind noncovalently to an epitope of a gp41 fusion intermediate and thereby retard gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell. In this regard, applicants reiterate the dicta of *In re Wands* quoted hereinabove that "a considerable amount of experimentation is permissible, if it is merely routine."

Applicants note the Examiner's citation of Gait and Karn (1995), as summarizing the prior art, and in particular their statement that "effective regimens for the prevention of the progression to clinical symptoms of acquired immune deficiency syndrome (AIDS) and the treatment of AIDS patients have not yet been developed." Applicants respectfully submit that reliance on Gait and Karn (1995) in this context is without merit for the following reasons: (1) Gait and Karn (1995) was published more than four years before the January 28, 2000 priority date of the subject application. Applicants note that in a field of research as active as anti-HIV therapeutics, statements on the state of the art rapidly become outdated and obsolete. In particular, applicants maintain that the identification in 1995 of obstacles to the development of anti-HIV therapeutics does not mean that such obstacles would not have been overcome as of 2000. Experience has shown that, on the contrary, the development of new technologies and approaches, for example, as described in the subject application, invariably serves to overcome the identified difficulties; and (2) Gait and Karn (1995) relates to the use of reverse transcriptase and protease inhibitors as antiviral drugs. Applicants respectfully submit that the teaching of Gait and Karn (1995) is irrelevant to the present invention which does not pertain to or involve a reverse transcriptase or protease inhibitor.

In view of the above remarks, applicants maintain that the specification as filed satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, with regard to pending claims 1, 5-13, 19, 21-26, and 42-45, and request that the Examiner reconsider and withdraw this ground of rejection.

Claims 20 and 27

The Examiner stated that for the same reasons given above, claims 20 and 27 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that the claims are drawn to a composition comprising an admixture of two compounds which inhibit HIV-1 entry into CD4+ cells, wherein the compounds are non-peptidyl agents. The Examiner also stated that the specification of the instant application defines the non-peptidyl agent as a compound which "does not consist in its entirety of a linear sequence of amino acids linked by peptide bonds [but that a] non-peptidyl agent may, however, contain one or more peptide bonds" (citing page 16, lines 10-15 and page 18, lines 13-16). The Examiner further stated that applicants are claiming that non-peptidyl agents inhibit HIV entry by binding to gp120 or gp41 but that, however, the state of the art does not support that such an agent or mechanism is known.

In response, applicants respectfully traverse the rejection of claims 20 and 27 under 35 U.S.C. §112, first paragraph.

In responding to the instant rejection, applicants hereby incorporate by reference the remarks made above in response to the "enablement rejection" of claims 1, 5-13, 19, 21-26 and 42-45. Applicants reiterate that the RET assay enables a skilled artisan to identify, without resort to undue experimentation, non-peptidyl compounds that inhibit fusion of HIV-1 env glycoproteins to CD4+ cell membranes. Applicants maintain, therefore, that the invention claimed in claims 20 and 27 is fully enabled by the specification as filed. Accordingly, applicants respectfully request that the instant rejection of claims 20 and 27 be withdrawn.

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1, 5-10, 12, 13, 19, 21-23 and 42-45 under 35 U.S.C. §102(b) as allegedly anticipated by Allaway *et al.* (U.S. Patent No. 5,817,767; herein "Allaway"). The Examiner stated that claim 1 is drawn to a composition which comprises an admixture of two compounds, one of which inhibits the binding of gp120 to CD4, and the other inhibits gp41 binding conformation, wherein the ratio of compounds ranges from about 100:1 to about 1:100. The Examiner also stated that claims 5-7 are drawn to a protein that binds either gp120, gp160 or gp140. The Examiner further stated that claims 8-10, 12 and 13 are drawn to the composition of claim 1, wherein the compound that retards gp120 binding to CD4 is an antibody, specifically a human, humanized or chimeric monoclonal antibody, comprising the variable domain of the antibody or CDR portion of the antibody. The Examiner additionally stated that claims 19 and 21-23 are drawn to the composition of claim 1, wherein the compounds are peptides and antibodies. Further, the Examiner stated that claims 42-45 are drawn to method of inhibiting HIV-1 infection in a cell in a subject by administering the composition of claim 1.

In addition, the Examiner stated that Allaway discloses compositions containing CD4-based immunoconjugates and antibodies specific for the envelope glycoprotein of HIV, wherein the CD4-based immunoconjugates comprise a portion from CD4 conjugated to a heavy or light chain region from IgG2 (citing the abstract). The Examiner also stated that the heavy or light chains are encoded by vectors having ATCC Accession numbers 75193 and 75194 (citing the abstract). The Examiner further stated that Allaway also teaches that the ratio of compounds CD4-based proteins to antibodies is between about 0.01 and about 100 (citing col. 4, lines 33-43). The Examiner stated that also taught are antibodies that form a complex with an epitope (in the V3 loop) present on HIV-1 gp120 envelope glycoprotein and antibodies that form a complex with an epitope present on HIV-1 gp41 envelope glycoprotein (citing col. 8, lines 43-47). The Examiner also stated that Allaway teaches human, murine, or humanized murine anti-gp120 and anti-gp41 monoclonal antibodies (citing col. 14, lines 44-53). The Examiner further stated that composition is an HIV-neutralizing composition comprising a carrier, said composition being designed to treat a subject by administering the composition to reduce the rate of spread of HIV-1 infection in a subject (citing col. 5, lines 39-59). The Examiner concluded that, therefore, Allaway anticipates the claims.

In response, applicants respectfully traverse this rejection.

Applicants note that independent claims 1, 44 and 45 specify that one of the compounds, present in the claimed composition or used in the claimed method, retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate. Since all of the other claims rejected under 35 U.S.C. §102(b) depend from claims 1, 44 or 45, they necessarily recite all the limitations of claims 1, 44 or 45.

Applicants note that, by contrast, Allaway does not teach that an antibody which binds to gp41 must bind to an epitope on a gp41 fusion intermediate. Instead, Allaway teaches that the antibody is capable of forming a complex with an epitope present on HIV-1 gp41 envelope glycoprotein, and that the antibody may be the monoclonal antibody designated 2F5 (see col. 8, lines 48-54).

As disclosed in the specification of the subject application, during fusion, gp41 adopts transient conformations that include a prehairpin fusion intermediate that ultimately folds into a conformation capable of mediating fusion (page 1, lines 24-26). Further, the specification discloses at page 5, line 32 to page 6, line 14 that recent studies (citing LaCasse *et al.* [1999] "Fusion-competent vaccines: broad neutralization of primary isolates of HIV." *Science* 283: 357-362) have demonstrated the possibility of raising antibodies against HIV-1 fusion intermediates. The specification also discloses that antibodies raised against structures such as gp41 fusion intermediates that are highly conserved and transiently exposed during HIV-1 entry demonstrated unprecedented breadth and potency in inhibiting primary HIV-1 isolates regardless of their coreceptor usage. Importantly, the specification further teaches that this class of antibodies does not include the anti-gp41 monoclonal antibody known as 2F5, which interacts with an epitope that is constitutively presented on virus particles prior to fusion. Applicants maintain, therefore, that the class of gp41-binding antibodies taught by Allaway, including 2F5, is different from the compounds claimed in the subject application which bind to an epitope on a gp41 fusion intermediate.

Applicants emphasize that a finding of anticipation requires a reference to disclose all the elements of the claimed invention. Applicants respectfully submit that because the gp41-binding antibodies taught by Allaway are different from the compounds which binding noncovalently to an epitope on a gp41 fusion intermediate as claimed in the subject application, Allaway fails to teach each and every element of the rejected claims, and hence fails to anticipate the claims. Applicants therefore request that the Examiner reconsider and withdraw this ground of rejection.

Rejections under 35 U.S.C. §103(a)

Claim 11

The Examiner rejected claim 11 under 35 U.S.C. §103(a) as allegedly unpatentable over Allaway, as applied to claims 1, 5-10, 12, 13, 19, 21-23 and 42-45. The Examiner stated that claim 11 is drawn to the composition of claim 1 wherein the antibody portion is the Fab fragment. The Examiner noted that Allaway teaches the composition of claim 1 but is silent on the Fab portion of the antibody as a compound in the composition. The Examiner stated that, however, it is well known in the art that the Fab fragment is the portion which binds epitopes because it contains the variable regions. The Examiner further stated that one of ordinary skill in the art would have been motivated to use the portion of the antibody that binds epitopes and would have had a reasonable expectation of success given the nature of the Fab fragment.

In response, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness of claim 11.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate, first, that the cited reference teaches or suggests every element of the claim; second, that one of ordinary skill in the art would have been motivated to make the invention based on the teachings of the cited reference; and third, that there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the Examiner has failed to satisfy all three prongs of the requirements for establishing a *prima facie* case of obviousness. First, as discussed hereinabove in response to the rejections under 35 U.S.C. §102(b), Allaway does not disclose the limitation that a compound which binds to gp41 must bind to an epitope on a gp41 fusion intermediate. By contrast, instant claim 11, which depends indirectly from claim 1, contains this limitation. Applicants maintain, therefore, that since Allaway does not teach or suggest this element which is present in claim 11, the Examiner fails to satisfy the first requirement for establishing a *prima facie* case of obviousness.

Second, applicants maintain that Allaway, in combination with routine skill, does not provide any suggestion or motivation to make a composition comprising a compound which binds to an epitope on a gp41 fusion intermediate. Thus, the Examiner fails to satisfy the second requirement for establishing a *prima facie* case of obviousness.

Third, Allaway does not provide any expectation of success in making a composition comprising a compound which binds to an epitope on a gp41 fusion intermediate.

Accordingly, since the Examiner has not satisfied the second requirements for establishing a *prima facie* case of obviousness, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 11 as obvious over Allaway.

Claims 24 and 26

The Examiner rejected claims 24-26 under 35 U.S.C. §103(a) as allegedly unpatentable over Allaway as applied to claims 1, 5-10, 12, 13, 19, 21-23 and 42-45 above, and further in view of Bolognesi *et al.* (U.S. Patent No. 5,464,933; herein, "Bolognesi"). The Examiner stated that the claims are drawn to the composition of claim 1, wherein the compound that binds the epitope on gp41 is a peptide, selected from the group consisting of T-20, DP107, N34, C28 and N34. The Examiner also stated that Allaway teaches the composition of claim 1, but is silent on the peptides of the instant invention. The Examiner further stated that Bolognesi teaches peptides that exhibit potent anti-HIV transmission activity (citing the abstract). The Examiner additionally stated that one of the peptides disclosed is DP-178, a gp41-derived peptide, which corresponds to T-20 of the instant invention (citing col. 5, lines 19-29, and figure 1 of Bolognesi). The Examiner also stated that one of ordinary skill in the art would have been motivated to substitute DP-178 for the antibody of Allaway because they perform the same function of binding gp41 to inhibit HIV-1 entry into CD4+ cells. The Examiner further stated that one of ordinary skill would have had a reasonable expectation of success given the identical function of the antibody of Allaway and the peptide of Bolognesi. The Examiner concluded that, therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In response, applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's assertion that Allaway teaches the composition of claim 1, but is silent on the peptides of the instant invention. As applicants note above, Allaway does not disclose the compositions claimed in the instant invention since, unlike in the instant claims, there is no disclosure in Allaway of any composition wherein one compound must necessarily bind to an epitope on a gp41 fusion intermediate. Thus, Allaway teaches neither the composition of claim 1 nor the peptides of the instant invention.

Applicants maintain, therefore, that since the cited Allaway and Bolognesi references in combination do not teach or suggest this element which is present in claims 24 and 26, the Examiner fails to satisfy the first requirement for establishing a *prima facie* case of obviousness. In addition, since Allaway and Bolognesi in combination do not provide any suggestion or motivation to make, or any expectation of success in so making, a composition comprising a compound which binds to an epitope on a gp41 fusion intermediate, applicants maintain that the Examiner also fails to satisfy the second and third requirements for establishing a *prima facie* case of obviousness.

Thus, applicants respectfully submit that the rejection of claims 24 and 26 as obvious over Allaway in view of Bolognesi should be withdrawn.

Double Patenting

The Examiner rejected claims 1, 5-13, 19, 21-26 and 42-45 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of U.S. Patent No. 6,692,745 B2. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are a genus of the patented species claims, rendering the genus claims obvious. The Examiner also stated that the patented species claims are drawn to a composition and method of inhibiting HIV-1 in a cell, wherein the composition comprises two peptidyl compounds. The Examiner further stated that the instant claims are drawn to a composition and method of inhibiting HIV-1 in a cell, wherein the composition comprises two compounds. The Examiner concluded that the claims are therefore obvious over the patented species claims.

In response, applicants respectfully traverse this obviousness-type double patenting rejection. Nevertheless, to advance prosecution of the subject application and without conceding the correctness of the Examiner's position, applicants will consider filing a terminal disclaimer if the claims under examination are otherwise allowable.

Conclusion

In view of the remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the June 4, 2004 Office Action, and earnestly solicit allowance of all claims pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed fee of FOUR HUNDRED AND NINETY DOLLARS (490.00) for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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